Docket No.: Serial No. Title: Inventor(s)

ISIS-5030

Oligoribonucleotides and Ribonucleases for Cleaving RNA

Stanley T. Crooke Gwilym Attwell

Attorney Phone No.: 215 568-3100

Attorney: Sheet 1 of 2

ptistehalberlgiopnnirllakapternipnndlik - - ghnorlemlødsviqlivsdplyrrppyhhrghmsllrtslusnotorvoddigfte katkmppklpbiodlatrapyehkstikdkvylsgsbminahnbrlbflgdsilnsvatlitnkfpdysgoqlstlrnnlysnbqikqmsimvnffr pVLQKLTEFEBAIGVIFTHVRLLARAFTLRTVGFNHLTL - - CHNQRNEFLGDSIMQLVATSYLFIHFPDHHEGHLTLLRSSLVNNRTQAKVAEELGMQE seypppleptrseklkeqvpmiisravelyppnqsnpmelldihnerleflodsfpnlfttrifskppqmdggslsklrakfvqnesadkfarlvgfdk

Tuman

Morm

PAC

RNT SNC ННИНИНН......------<u>ВВВВВ</u>

mnpivinrlorkloytenhoelloqalthrsass-----khnerleflodsilsyvianalyhrpprodsgdmsnmratlvronylarlarefelge

Yalthdktkrpv----glrtktladliesflaalytdkdlekvhtf-mnvcffprikkeflingdmndpksgliggccltlrte-----gkepdiplikkt FVIK-APYKTPE-----LKLKDKADLVBAFIGALYVDRGIEHCRAF-IRIVFCPRLKHFIESEKMNDAKSHLOOWCLAMRDP-----SSSEPDMFEYRV

Human

Norm

PAC

ilvisysaekdo---irksokvladtfervigalildgobetafowysrilopkianitvorpidklakskiffkysti-------------------------------KIKTIYFDLKDBNSHFQNGKLKLYADVFBAYLGGLMEDDPRNNLPK.--IRKWLRKLAKPVIBBATRHQVALBKTDKLDMNAKRQLYSLIGYASLRLHYVT CLRLGPGELKSG---GFRRESILADTVEALIGGVFLDSDIQTVEKL-ILNNYQTRLDEISPGDKQKDPKTRLQEYLQ------

SNC RNT

lotvopshartytv-avyekgeriocgkopsiqqaemgaandalekynppqmahqkrfigrkyrqelkemfwerehqerepdetedikk (endl374) lgiegptnnrifki - avyykgkrlasaaesnvhkaelrvaelalanjesmsfskkkaknnsnmrrrlegdtsd (end412)

Human

Norm

PAC RNT

VKKPTAVDPNSIVE-CRVGDGTVLGTGVGRNIKLAGIRAAENALRDKKMLDFYAKQRAAIPRSESVLKDPSGKNKKRKFSDTS (end471) VDGAGGSAEGYVI--ACIFNGKEVARAWGANQKDAGSRAAMQALEVLAKDYSKFAR (end363)

vovrgeahdoeftihcovsglsepvvgtgssrrkaeqaaaeqalkklele (end226) RNC

FIGURE

LOGYGIES DEFOOL

MMQGNTCHRMSFHPGRGCPRGR

Tuman Tuman fuman Tuman fuman fuman

Tuman

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Title. (Inventor(s):

Attorney Phone No . 215 568-3100

Attorney: Gwilym Attwell Sheet 2 of 2

SPERLKHYDDHRHRDHSHGRGERHRSLDRRERGRSPDRRRQDSRYRSDYDRGRTPSRHRSYERSRERERERHRHRDNRRSPSLERSYKEYKRSUG LSVVPEPAGCTPELPGELIKNTDSWAPPLEIVNHRSPSREKKRARWEBEKDRWSDNQSSGKDKNYTSIKEKEPEETMPDKNEBEEEELLKPVWIRCTHS entyssdpmdqvgdstvvgtsrlrdlydkfeeelgsrqekakaarppweppktkldedlesssbesecesdedstcssssbedvfdvlaeikrkkahpdr LHDELWYNDPGOMNDGPLCKCSAKARRTGIRHSIYPGEEAIKPCRPMTNNAGRLFHYRITVSPPTNFLTDRPTVIEXDDHEYIFEGFSMFAHAPLTNIP LCKVIRFNIDYTHFI EEMMPBNFCVKGLELFSLFFRDILELYDWNLKGPLFEDSPPCCPRFHFMPRFVRFLPDGGKEVLSMHQILLYLLRCSKALVP seelanmlomeelemokvaeeckgmivtupgtkpssvridoldreofupdvitffiivhfgirpaolsvagdpovoklmksvvklrhllanspkvkgtd K QKLA QREEAL QKI RQKNTMRREVTVELSS QGFWKTGIRSDVCQHAMMLP VLTHHIRYHQCLMHLDKLI GYTFQDRCLLQLAMTHP SHHLNFGMNPDHA 3GHGARPSABSFRPQNLRLLHPQQPPVQYQYEPBSAPSTTFSNSPADNFLPPRPDFVPFPPPMPPSAQGPLPPCP1RPPFPNHQMRHPFPVPPCFFPMP ppmpcpnnppvpgadpgqgtfpfmadppsmppdppvmpqqvnxqxppgxshinfppssfnsfqnnpssplpsannsssphfrhldpyfllppyfberr

rnslsncgtropkygdrvhhmhmrkkgintlinimsrlgoddptpg--rinhnerleflgdavvefltsvhlyylfpsleegglatyrtalvonghla

8000000000000000

Tuman

Tuman Tuman Tuman

Worm

SAC K

mslfnimkgtsggepilhnerleylgdavvelivshhlyfmlthhfegglatyrtalvonrnla MGRFKRHHEGDSDSSSSASDSLSRGRRSLGHKRSSHIKNRQYY MGSKVAGKKKTONDNKLDNENGSQQRENINTKTLLKGNLKISNYKYLEVIQLEHAVTKLVESYNKIIELSPNLVAYNEAVNNODRVPVQLLPSLSRYQL

MLAKKLE-LDPFML-YAHGPDLCRESDLRHAMANCFEALIGAVYLEGGLEEAKQLFG--RLL-FNDPDLREVWLNYPLHPL-Q-LQEPNTDRQLIETS TLAKNCR-LDE-MLQYSHGADLINVAEFKHALANAFEAVMAAIYLDGGLAPCDVIFS---KAMYGHQPVLKEKWDHINEHEL--KREDPQGDRDLSFIT ILEKKIRKLMFAMKALLEETKHST--------KDDVNLVIPGSTWSHIEGVYEMLKSRHDRONEPVIEEPSSHPKNOKNOEPTSEEFEE Human

Worm PAC EM2

KLAAELKTLHDLKKDAILTEITDYENEFDTEGKQ-----PILGEISKADMEKLEKLEGVKREKREKIDVNVYENLNEKEDEEEDEGEBSYDPTKAGDIV

FIGURE 1 (Continued)